

“Does the exception prove the rule? - A comparative study of supramolecular synthons in a series of lactam esters”

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Abstract

In this paper a series of simple lactam esters and carboxylic acids is studied with respect to their overall conformation and hydrogen bonding patterns. In total, eight lactams featuring N_α -substitution have been synthesized. Additionally, the molecular structures of related lactam esters have been considered. The length of the amide bonds does not seem to be majorly influenced by different substituents unless the electron withdrawing *N*-Boc-protection group is introduced, resulting in a higher susceptibility towards hydrolytic ring opening. As known from other lactams, the N_α ester moiety of the title compounds can be in an axial or equatorial conformation. Smaller ester groups were found to prefer equatorial positions, while larger ones occupy axial sites. *N*-substitution seems to promote axial conformations of the respective N_α group, with enantholactams being the only studied exception. In addition to the two common amide packing motifs, i.e. the $R_2^2(8)$ amide dimer ($NH\cdots O/NH\cdots O$) and the $C(4)$ amide chain, a third graph-set was found: the $R_2^2(8)$ $NH\cdots O/CH\cdots O=C$ heterodimer. In general, there seems to be a tendency for medium-sized lactams as well as lactams with small esters to form $R_2^2(8)$ amide dimers. Larger esters and enantholactam esters lead to $C(4)$ amide chains. In this respect the formation of $R_2^2(8)$ $N-H\cdots O/C-H\cdots O=C$ heterodimers should be seen as a remarkable exception.

Keywords:

Lactam synthesis

Hydrolytic lability

Hydrogen bonding synthon

Reactive conformation

Conglomerate

INTRODUCTION

Lactams, *i.e.* cyclic amides, are a prominent class of heterocycles and can be considered as oxo derivatives of the respective cyclic amines. However, their trivial names are used much more commonly (Figure 1). For many years lactams have widely been employed in industry^{1,2} and in the synthesis of more advanced compounds.³⁻⁶ Moreover, lactams occur in natural products chemistry^{7,8} and are deployed as final APIs with the β -lactam antibiotics as the most prominent example.⁹ Despite being first described over one century ago, research on physical and chemical properties of lactams is still highly rewarding. Studies on their reactivity, thermodynamic and kinetic stability and their conformational behavior contribute not only to chemistry, though also to adjacent disciplines like material science and biology. A typical characteristic of lactams is the existence of *cis* and *trans* forms resulting from different dihedral angles of the amide bond.¹⁰ As observed for open amides, lactams also possess partial C-N double bond character, which goes in hand with resonance stabilization. While the amide bond lengths for small and medium-sized lactams (ring sizes 4-9) are rather consistent,¹¹ their hydrolytic stability is not with the four and six membered rings being hydrolyzed significantly faster.¹²

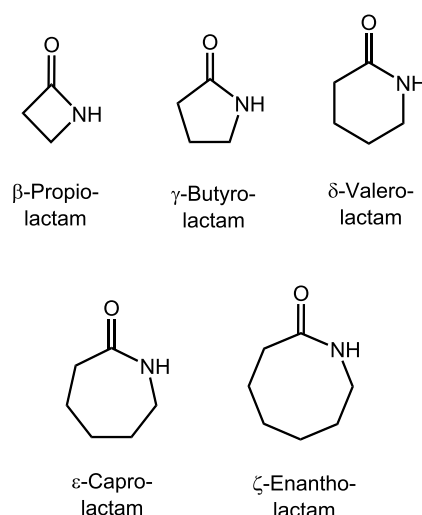


Figure 1. Nomenclature of small and medium sized lactams (trivial names).

Comparative studies on monocyclic lactams and especially simply substituted derivatives are unsatisfyingly rare.¹³⁻¹⁸ As part of our ongoing studies on bridged lactams¹⁹ we became interested in a series of small and medium-sized lactams featuring a carboxylic acid or a respective ester in the N_α position. In detail we discuss here the synthesis and the X-ray structures of pyroglutamates **1** (*iso*-propylester) and **2** (*tert*-butylester), pyrohomoglutamic acid methyl ester (**3**) and its respective acid (**4**), the N_α -disubstituted caprolactam²⁰⁻²⁵ **5** and the three enantholactam^{26,27} esters **6-8** (Figure 2); additionally, we deliver full analytical characterization. Some of the title compounds are already known as useful building blocks and/or are part of biologically active compounds, such as pyroglutamic acid,^{28,29} *iso*-propyl pyroglutamate (**1**),³⁰⁻³² *tert*-butyl pyroglutamate (**2**)³³⁻³⁷ and pyrohomoglutamic acid (**4**)^{38,39} and enantholactam **7**.⁴⁰

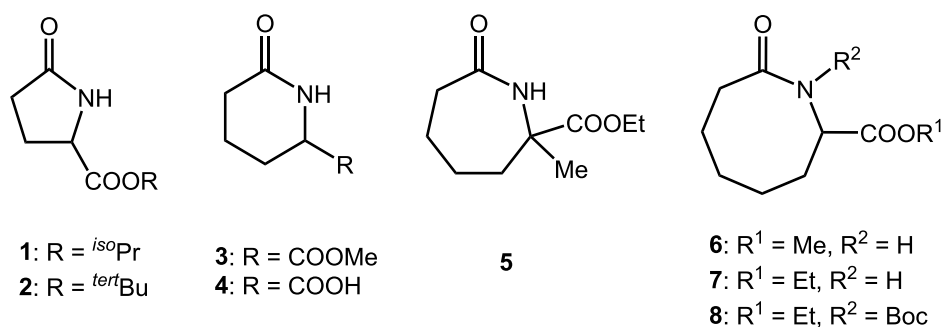


Figure 2. Title compounds 1-8.

The aim of this study was to learn how the ring size of the respective lactam and the nature of the carboxyl pendant affect the overall conformation and the hydrogen bonding pattern in the crystal packing. In general, R₂(8) amide dimers and C(4) chains are typical graph-set descriptors found in lactam structures. However, for some title compounds we found alternative supramolecular synthons. For comparison reasons, we also included the molecular structures of related lactam derivatives in our considerations. As a result, we are able to present a comprehensive study on the solid state behavior of this synthetically useful type of compound and discuss the general influence of ring size and substitution pattern on the COOH and COOR moieties at the N_α position of lactams. The respective moieties can either adopt an axial or an equatorial site, which is of crucial importance for their reactivity e.g. in transannular cyclization reactions.^{19,41,42} For steric reasons only ester groups in axial positions will allow such conversions (Figure 3). Despite the axial and the equatorial conformation are connected via equilibrium in solution, the molecular structures of the title compounds deliver valuable insights into their reactive conformation and give most beneficial information on distances and interactions in and between the molecules.

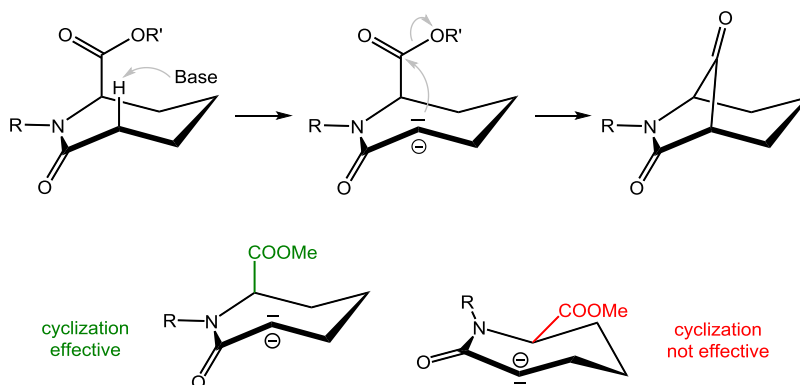


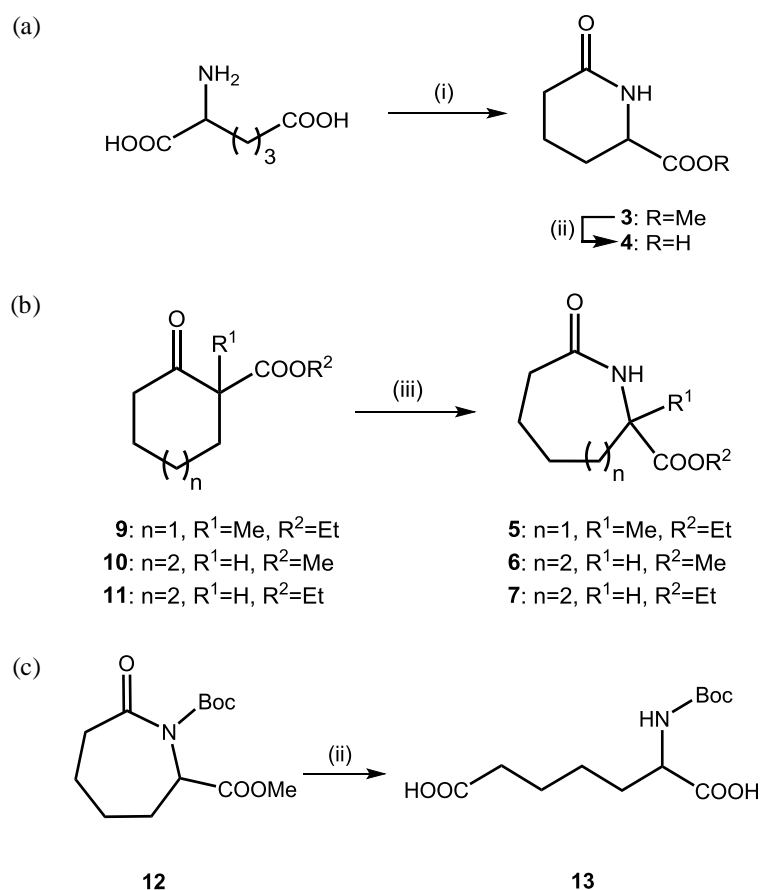
Figure 3. Dieckmann reaction of caprolactam esters as a reported example of a transannular cyclization.¹⁹

EXPERIMENTAL SECTION

Synthesis of lactams 1-8. Butyrolactams **1** and **2** were synthesized from pyroglutamic acid and the respective alcohol via Steglich esterification. By way of interest, the *iso*-propyl ester could be isolated in a much higher yield than the respective *tert*-butyl ester (68 % vs. 9 %). The respective methyl ester (**3**) was prepared by direct cyclization of 2-aminoadipic acid in methanol and thionylchloride (58 % yield); saponification resulted in lactam acid **5** (79 %) (Scheme 1a). Title compounds **5-7** were synthesized via Schmidt rearrangement^{43,44} from the

respective cycloketones (**9-11**)⁴⁵⁻⁴⁸ in moderate to good yields (35-72 %) (Scheme 1b). *N*-Boc-protection of ethyl ester **7** gave enantholactam **8** in 83 % yield. When we tried to saponify the Boc-protected caprolactam **12**⁴⁹ using LiOH/H₂O₂, ring opening was observed and the respective Boc-protected adipic acid **13** could be recovered (Scheme 1c).

Scheme 1. (a) Syntheses of Valerolactams **3** and **4**. (b) Syntheses of Lactams **5-7** via Schmidt reaction. (c) Hydrolysis of Boc-protected caprolactam **12**.^a



^a Reaction conditions: (i) MeOH, SOCl₂, rt; (ii) LiOH, H₂O₂, THF/H₂O (1:1), rt; (iii) NaN₃, H₂SO₄, CHCl₃, 50 °C.

Materials and methods. Melting points were determined on a Zeiss Axio Vision microscope fitted with a Linkam THMS600 stage. Infrared spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer. All wave numbers are given in cm⁻¹. Mass spectra were recorded on a TSQ Endura Mass Spectrometer. High-resolution mass spectra were recorded on a Thermo Exactive Plus Orbitrap Mass Spectrometer with a Dionex UltiMate 3000 Quaternary RSLCnano System. Proton (¹H, 500 MHz) and carbon (¹³C, 125 MHz) nuclear magnetic resonance experiments were performed on a Bruker Avance 500. NMR samples were prepared in CDCl₃ and MeOD-d₄ using TMS as an internal chemical shift standard. Reactions were followed with TLC (254 μm SiO₂ 60-F), visualization accomplished by KMnO₄-staining. Column chromatography was performed on 230-400 mesh, 0.063-0.040 mm).

All reactions that required water free reaction conditions were performed under a nitrogen atmosphere. Dry solvents were purified over activated aluminum oxide. Commercially available starting materials were used as received by Fluorochem. Ethyl 1-methyl-2-cyclohexanonecarboxylate (**9**) was synthesized from ethyl 2-cyclohexanone-carboxylate, methyl iodide and potassium carbonate according to a literature procedure.⁴⁵ Methyl⁴⁷ (**10**) and ethyl 7-cycloheptanonecarboxylate⁴⁸ (**11**) were synthesized from cycloheptanone using the respective dialkylcarbonate and sodium hydride. The synthesis of caprolactam ester **12** has been described earlier.¹⁹

Preparation of pyroglutamates 1 and 2 (Steglich esterification). Commercially available pyroglutamic acid (1 eq.) was dissolved in dry CH₂Cl₂ (10 ml) followed by the addition of 4-dimethylaminopyridine (DMAP, 100 mg, 0.82 mmol) and the respective alcohol (4 eq.). The mixture was cooled to 0 °C and *N,N'*-dicyclohexylcarbodiimide (DCC, 1.6 g, 7.75 mmol) were added. The mixture was stirred for 24 h. The resulting suspension was filtered and the filtrate washed with 0.5M hydrochloric acid. The organic layer was dried over MgSO₄, concentrated *in vacuo* and purified by column chromatography (cyclohexane : EtOAc = 2 : 1) to give the desired esters.

(*RS*)-*iso*-Propyl pyroglutamate (**1**). Synthesized using 1.0 g of the starting material. Yield: 900 mg (5.26 mmol, 68 %); white crystalline solid. TLC: *R_f* = 0.31 (EtOAc). Mp = 86 °C.

(*RS*)-*tert*-Butyl pyroglutamate (**2**). Synthesized using 1.0 g of the starting material. Yield: 119 mg (0.64 mmol, 9 %); white crystalline solid. TLC: *R_f* = 0.26 (EtOAc). Mp = 97 °C; lit.⁵⁰: 93 °C (ether/petroleum ether).

Full analytical data of the respective (*S*)-enantiomers of **1** and **2** can be found in the literature.⁵¹

(*RS*)-Methyl 6-oxo-piperidinecarboxylate (**3**). Methanol (40 ml) was cooled to -10 °C before adding thionylchloride (3.4 ml, 17.4 mmol), followed by the addition of commercially available 2-aminoadipic acid (1.00 g, 6.88 mmol). The resulting mixture was stirred overnight, the solvent removed *in vacuo* and the residue dissolved in saturated aq. NaHCO₃. The aqueous phase was extracted three times with ethyl acetate, dried over MgSO₄ and the solvent removed *in vacuo* to give the desired product as a viscous oil, which crystallized after several days at room temperature. Yield: 572 mg (4.00 mmol, 58 %); white crystalline solid. TLC: *R_f* = 0.23 (EtOAc). Mp = 65 °C. Full analytical data of the (*S*)-enantiomer of **3** can be found in the literature.⁵²

(*RS*)-6-Oxopiperidinecarboxylic acid (**4**). Methyl ester **3** (300 mg, 1.91 mmol) was dissolved in a mixture of THF (15 ml) and water (15 ml). Subsequently, LiOH (183 mg, 7.64 mmol) was added, followed by H₂O₂ (30 % in water, 65 µl, 2.10 mmol). The mixture was stirred for 24 h, then the pH adjusted to 3 with 0.5M hydrochloric acid and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and the solvent was removed *in vacuo* to give a viscous, colorless oil, which crystallized after several hours to a crystalline product. Yield: 217 mg (1.52 mmol, 79 %). Mp = 178 °C; lit.⁵³: 178-179 °C. ¹H NMR: (500 MHz, MeOD-*d*₄) δ 3.99 (t, ³*J* = 6.3 Hz, 1H, *H*₁), 2.40 (t, ³*J* = 7.2 Hz, 2H, *H*₄), 2.05-1.89 (m, 2H, *H*₃, *H*₂), 1.85-1.67 (m, 2H, *H*_{3'}, *H*_{2'}). ¹³C NMR: (125 MHz, MeOD-*d*₄) δ 175.1 (*C*₅), 170.1 (*C*₆), 52.3 (*C*₁), 32.6 (*C*₄), 29.5 (*C*₂), 20.0 (*C*₃). IR (ATR) *ν*_{max}: 3202 (*CONH*); 2933 (*CH*-aliphatic); 1720 (*C=O*, ester); 1642 (*C=O*, lactam); 1582; 1489; 1453; 1408; 1372; 1329; 1297; 1246; 1222; 1172; 1098; 1036; 940; 873; 799; 765; 737; 710; 620; 538; 495. HR-MS: calculated 144.0655 g/mol [*MH*]⁺, found 144.0643 g/mol.

General synthetic procedure for the synthesis of lactams 5-7 (Schmidt reaction). The respective ketone (1 eq.) was dissolved in CHCl₃ (30 ml), followed by the addition of concentrated H₂SO₄ (15 ml). Finally, sodium azide (1.2 eq.) was added carefully. The mixture was then stirred gently and heated to 50 °C for 6 h. The cooled mixture was poured on crushed ice (200 g) and concentrated aq. NH₃ was added until the aqueous phase reacted basic. The

layers were separated and the aqueous layer was washed three times with CHCl_3 . The combined organic layers were dried over MgSO_4 , the solvent was removed *in vacuo* and the residue was purified using column chromatography [SiO_2 ; ethyl acetate] to give the desired lactams **5-7**.

Ethyl 2-methyl-7-oxoazepanecarboxylate (5). Synthesized using 1.40 g ethyl 1-methyl-2-cyclohexanonecarboxylate (**9**) as starting material. Yield: 1.12 g (5.62 mmol, 74 %); off-white crystalline solid. TLC: $R_f = 0.28$ (EtOAc). Mp = 96.0 °C. ^1H NMR: (500 MHz, CDCl_3) δ 6.13 (br s, 1H, *NH*); 4.25 (q, $^3J = 7.1$ Hz, 2H, *H9*); 2.55-2.50 (m, 1H, *H3*); 2.37-2.26 (m, 2H, *H6*, *H3'*); 1.92-1.87 (m, 1H, *H4*); 1.76-1.68 (m, 2H, *H6'*, *H5*); 1.61-1.54 (m, 2H, *H4'*, *H5'*); 1.49 (s, 3H, *H11*); 1.31 (t, $^3J = 7.1$ Hz, 3H, *H10*). ^{13}C NMR: (125 MHz, CDCl_3 , δ [ppm]) 177.6 (*C2*); 173.8 (*C8*); 61.8 (*C9*); 59.7 (*C7*); 39.1 (*C6*); 37.6 (*C3*); 28.3 (*C11*); 26.4 (*C5*); 22.9 (*C5*); 14.2 (*C10*). IR (ATR) ν_{max} : 3198 (*CONH*); 3087 (*CONH*); 2974 (*CH-aliphatic*); 2936 (*CH-aliphatic*); 2859 (*CH-aliphatic*); 1730 (*C=O ester*); 1661 (*C=O lactam*); 1579; 1456; 1411; 1382; 1360; 1343; 1311; 1290; 1261; 1215; 1174; 1152; 1121; 1093; 1057; 1038; 1006; 954; 889; 879; 837; 803; 769; 757; 735; 718; 693; 656; 620; 576; 547; 510; 462. HR-MS: calculated 200.1286 g/mol $[\text{M}+\text{H}]^+$, found 200.1264 g/mol.

Methyl 8-oxoazocanecarboxylate (6). Synthesized using 1.0 g methyl 2-cycloheptanonecarboxylate (**10**) as starting material. Yield: 442 mg (2.39 mmol, 35 %); off-white crystalline solid. TLC: $R_f = 0.37$ (EtOAc). Mp = 89 °C; lit.⁵⁴: 80-82 °C. ^1H NMR: (500 MHz, CDCl_3 , δ [ppm]) 6.05 (br d, 1H, *NH*); 4.31-4.26 (m, 1H, *H8*); 3.79 (s, 3H, *H10*); 2.44-2.35 (m, 2H, *H3*, *H3'*); 2.05-1.99 (m, 1H, *H7*); 1.92-1.72 (m, 4H, *H5*, *H6*, *H4*, *H4'*); 1.68-1.61 (m, 1H, *H7'*); 1.57-1.42 (m, 2H, *H5'*, *H6'*). ^{13}C -NMR: (125 MHz, CDCl_3 , δ [ppm]) 175.3 (*C2*); 172.1 (*C9*); 54.9 (*C10*); 52.7 (*C8*); 36.2 (*C3*); 33.6 (*C7*); 27.9 (*C4*); 25.8 (*C5*); 24.2 (*C6*), IR (ATR) ν_{max} : 3365 (*CONH*); 2922 (*CH-aliphatic*); 2856 (*CH-aliphatic*); 1732 (*C=O ester*); 1650 (*C=O lactam*); 1488; 1429; 1397; 1362; 1334; 1309; 1256; 1216; 1158; 1030; 981; 951; 911; 887; 873; 822; 791; 765; 747; 720; 677; 638; 570; 516. HR-MS: calculated 186.1130 g/mol $[\text{M}+\text{H}]^+$, found 186.1110 g/mol.

Ethyl 8-oxoazocanecarboxylate (7). Synthesized using 1.0 g ethyl 2-cycloheptanonecarboxylate (**11**) as starting material. Yield: 627 mg (3.15 mmol, 54 %); viscous, colorless oil, which slowly crystallizes. $R_f = 0.23$ (EtOAc). Mp = 91 °C; lit.⁵⁵: 96-98 °C. ^1H NMR: (500 MHz, CDCl_3) δ 6.02 (br d, 1H, *NH*); 4.28-4.22 (m, 3H, *H1*, *H9*); 2.4-2.38 (m, 2H, *H6*, *H6'*); 2.02-2.00 (m, 1H, *H2*); 1.88-1.75 (m, 4H, *H3*, *H4*, *H5*, *H5'*); 1.64-1.47 (m, 3H, *H4'*, *H3'*, *H2'*), 1.30 (t, $^3J = 7.2$ Hz, 3H, *H10*), ^{13}C NMR: (125 MHz, CDCl_3) δ 175.3 (*C7*); 171.6 (*C8*); 61.9 (*C9*); 55.0 (*C1*); 36.3 (*C6*); 33.6 (*C2*); 27.9 (*C5*); 25.8 (*C3*); 14.1 (*C10*) IR (ATR) 3311 (*CONH*); 2937 (*CH-aliphatic*); 2867 (*CH-aliphatic*); 1730 (*C=O ester*); 1614 (*C=O lactam*); 1467; 1447; 1362; 1350; 1322; 1289; 1260; 1242; 1221; 1184; 1160; 1095; 1061; 1017; 947; 915; 800; 770; 753; 713; 654; 572; 513; 502, HR-MS: calculated 200.1281 g/mol $[\text{M}+\text{H}]^+$, found 200.1281 g/mol.

1-tert-Butyl 2-ethyl 8-oxoazocane-1,2-dicarboxylate (8). Enantholactam **7** (2.00 g 10 mmol) was dissolved in dry toluene (50 ml). DMAP (200 mg, 1.64 mmol), Boc_2O (6.55 g, 30 mmol) and *N,N*-diisopropylethylamine (DIPEA, 2.44 ml, 14 mmol) were added before the mixture was refluxed for 6 h. Subsequently, the reaction was quenched with water (15 ml). The layers were separated and the aqueous layer was extracted three times with toluene. The combined organic layers were dried over MgSO_4 , the solvent was removed *in vacuo* and the residue was purified using column chromatography [cyclohexane : EtOAc, 4 : 1] to give a yellow viscous oil, which crystallized after several days. Yield: 2.47 g (8.25 mmol, 83 %). $R_f = 0.16$ (cyclohexane : EtOAc = 1 : 4). Mp = 98 °C. ^1H NMR: (500 MHz, CDCl_3) δ 4.58 (dd, $J_d = 4.5$ Hz, $J_{dd} = 12.3$ Hz, 1H, *H1*); 4.21 (qq, $^2J_q = 7.1$ Hz; $^3J_{qq} = 21.3$ Hz; 2H, *H9*); 2.79-2.73 (m, 1H, *H6*); 2.58-2.53 (m, 1H, *H6'*); 2.25-2.18 (m, 1H, *H2*); 2.08-2.00 (m, 1H, *H2*); 1.96-1.90 (m, 1H, *H5*); 1.83-1.67 (m, 3H, *H5'*, *H4*, *H3*); 1.51 (s, 9H, *H13*, *H14*, *H15*); 1.45-1.37 (m, 2H,

H4', *H3'*); 1.28 (t, $^3J = 7.1$ Hz, 3H, *H10*), ^{13}C NMR: (125 MHz, CDCl_3) δ 177.0 (*C7*); 170.3 (*C8*); 151.9 (*C11*); 83.4 (*C12*); 61.5 (*C9*); 58.3 (*C1*); 38.1 (*C6*); 30.8 (*C2*); 29.1 (*C5*); 28.0 (*C13*, *C14*, *C15*); 27.1 (*C4*); 24.2 (*C3*); 14.1 (*C10*), IR (ATR): 2980 (*CH-aliphatic*); 2942 (*CH-aliphatic*); 2865 (*CH-aliphatic*); 2334; 1745 (*C=O ester*); 1713 (*C=O carbamate*); 1699 (*C=O lactam*); 1464; 1448; 1394; 1367; 1354; 1331; 1315; 1293; 1279; 1260; 1200; 1149; 1125; 1109; 1083; 1047; 1022; 988; 955; 932; 897; 850; 818; 766; 743; 708; 674; 592; 549; 526; 479, HR-MS: calculated 322.1630 g/mol $[\text{M}+\text{Na}]^+$, found 322.1623 g/mol.

2-[[1,1-dimethylethoxy)carbonyl]amino]heptanedioic acid (13). 1-*tert*-Butyl 2-methyl 7-oxoazepane-1,2-dicarboxylate (1.02 g, 3.57 mmol) was dissolved in 25 ml THF, LiOH (0.34 g, 14.2 mmol) dissolved in 25 ml water and 3.5 ml of H_2O_2 (30 % in water) were added and the resulting suspension was stirred for 24 h. The pH was adjusted to 3 with 1M HCl solution and aqueous solution was extracted three times with EtOAc. The combined organic layers were dried over MgSO_4 , the solvent was removed *in vacuo* to give the desired product as a white, crystalline solid. Yield: 0.748 g (2.72 mmol, 78 %). Mp = 118 °C (decomposition). ^1H NMR: (500 MHz, MeOH-d_4) δ 4.06 (dd, $J_d = 4.8$ Hz, $J_{dd} = 8.9$ Hz, 1H, *H2*); 2.30 (t, $^3J = 7.4$ Hz, 2H, *H6*); 1.82-1.79 (m, 1H, *H3*); 1.65-1.62 (m, 3H, *H5*, *H3'*); 1.44-1.43 (m, 11H, *H4*, *H10*) ^{13}C NMR: 176.0 (*C1*); 174.9 (*C7*); 156.8 (*C8*); 80.0 (*C9*); 53.5 (*C2*); 33.3; 31.2 (*C3*, *C6*); 27.3 (*C10*); 25.1; 24.2 (*C4*, *C5*). IR (ATR) ν_{max} : 3324 (*CONH*); 2976 (*CH-aliphatic*); 2936 (*CH-aliphatic*); 2859 (*CH-aliphatic*); 1729 (*C=O ester*); 1678 (*C=O lactam*); 1645; 1531; 1454; 1395; 1368; 1298; 1280; 1254; 1215; 1159; 1106; 1068; 1051; 1014; 886; 852; 819; 784; 762; 743; 684; 626; 579; 535; 459. HR-MS: calculated 276.1442 g/mol $[\text{M}+\text{H}]^+$, found 276.1424 g/mol. Some analytical data of the respective L-enantiomer of **13** has already been described in the literature.⁵⁶

Structural characterization. Crystals of **1**, **2**, **5**, **6** and **8** suitable for X-ray Diffraction were prepared by slow solvent evaporation of the respective solutions in ethyl acetate (**1**, **2**, **5**, **6**) or methanol (**8**). Compounds **3**, **4**, **7** and **13** were recovered as oils, which produced crystals suitable for X-ray diffraction after several days. Single crystal X-ray diffraction was performed at 173 K with a Bruker D8 Venture diffractometer using a $\text{Cu-K}\alpha$ source. Structure solution was carried out with *shelxs*⁵⁷ and structure refinement with *shelxl*⁵⁷ was finished using *ShelXle*⁵⁸ software. For selected crystallographic and structural refinement parameters, molecular torsion angles and information regarding non-covalent interactions see Tables S1-S7, Supporting Information. The crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre; CCDC numbers: 1839816 (**1**), 1839824 (**2**), 1839823 (**3**), 1839820 (**4**), 1839817 (**5**), 1839818 (**6**), 1839819 (**7**), 1839821 (**8**), 1872073 (**13**).

RESULTS AND DISCUSSION

Butyrolactams 1 and 2. In this series we synthesized four esters of pyroglutamic acid, viz. methyl,⁵⁹ ethyl,⁶⁰ *iso*-propyl (**1**) and *tert*-butyl (**2**). The methyl and ethyl ester could only be recovered as oils, while **1** and **2** could be crystallized, followed by the determination of their X-ray structure. *iso*-Propylester **1** adopts a slight envelope conformation with C2 deviating from the C4-N1-C1-C2 mean plane by 0.1962(19) Å (Figure 4a); this is quite low compared to the parent lactam (0.371 Å) (CSD code: NILYAI).⁶¹ The ester group of **1** is in an axial position, though it is debatable if a C4-N1-C1-C5 angle of -125.58(10)° justifies the differentiation into axial/equatorial in this specific case.

In the packing, two molecules of **1** related via an inversion center form an $\text{R}_2^2(8)$ amide dimer via N-H \cdots O hydrogen bonds. These typical arrangements, which are also found in the

respective parent lactam, are interconnected via C-H \cdots O interactions between C3 and the carbonyl oxygen featuring the graph set descriptor $R_2^2(8)$ (Figure 4b).

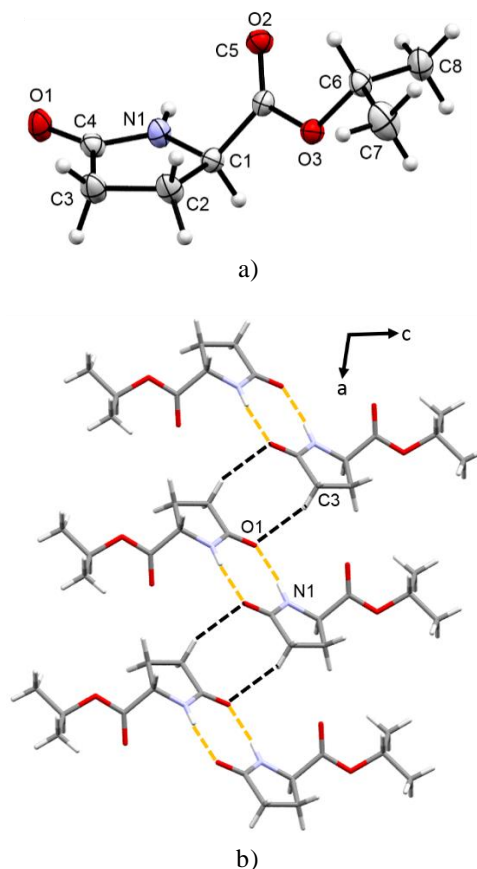


Figure 4. Molecular structure of *iso*-propyl ester **1** (a) and its packing diagram (b). Hydrogen bonds (orange) and C-H \cdots O contacts (black) are shown as broken lines.

The *tert*-butyl ester of pyroglutamic (**2**) crystallizes in the monoclinic space group; an orthorhombic polymorph of **2** has been described earlier (CSD code: DICXET).⁶² The asymmetric unit of the polymorph described here consists of one molecule in an envelope conformation, which is much more pronounced than those of the isopropyl ester (**1**). Carbon C2 deviates by 0.329(3) Å from the C4-N1-C1-C2 mean plane (Figure 5a); for the orthorhombic polymorph an ever larger bend (0.412 Å) is observed. The *tert*-butyl ester groups of **2** adopts an axial position with a C4-N1-C1-C5 angle of -102.50(16)°, which is comparable to the polymorph (100.4°) (Figure 5b). As expected, the methyl groups of the *tert*-butyl units avoid an eclipsed conformation with respect to the carbonyl group; this arrangement results in two intramolecular C-H \cdots O contacts.

The packing of *tert*-butyl ester **2** differs significantly from the one of the *iso*-propyl ester (**1**) discussed above. In both polymorphs of **2**, the amide units are engaged in C(4) chains consisting of N-H \cdots O hydrogen bonds; the strength of the interaction is thereby comparable with those of **1**. The N-H \cdots O chains are further connected by two C-H \cdots O contacts involving C1 \cdots O1 and C3 \cdots O3 featuring the graph-set descriptor $R_2^2(8)$. The resulting molecular bands are linked to their neighbors via a weaker C-H \cdots O contact. Towards the crystallographic *a* axis the molecular bands display hydrophobic interactions from the *tert*-butyl residues giving a layered overall packing (Figure 5c). When comparing the packing of **1** and both polymorphs

of **2**, the $R_2^2(8)$ C-H \cdots O dimers occur in all three packing diagrams, despite the generally more dominant amide hydrogen bonding pattern is changing from **1** to **2** (Figure S1, Supporting Information).

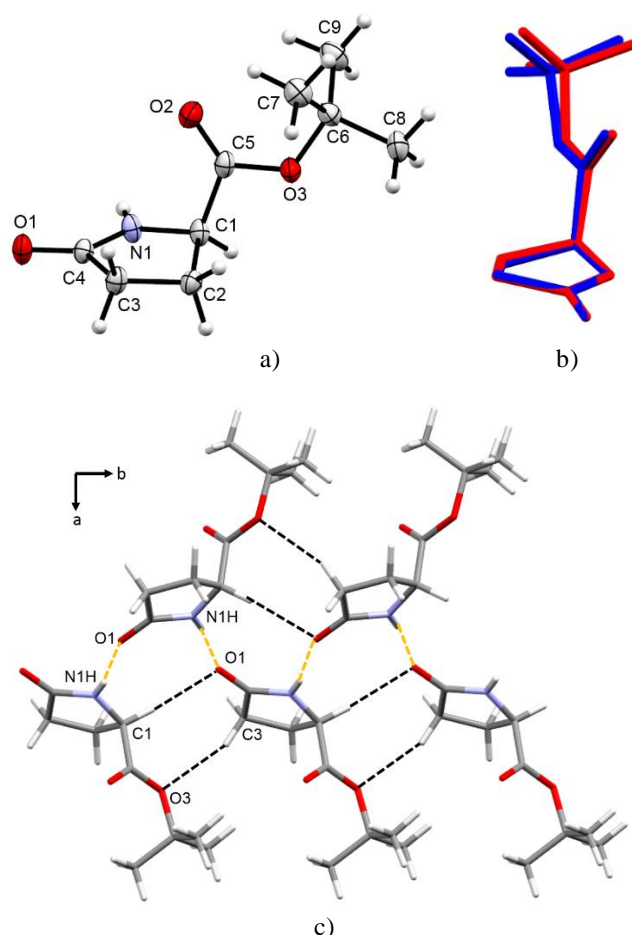


Figure 5. Molecular structure of *tert*-butyl ester **2** in the monoclinic polymorph (a) and the overlay of the **2** in the monoclinic (red) and orthorhombic space group (blue) (overlay of amide region) (b). Packing behavior of **2** displayed in direction of the *c* axis.

Valerolactams 3 and 4. The amide region of methyl ester **3** is more or less planar with atoms C2 and C3 deviating from planarity by 0.359(2) Å for C2 and 0.395(2) Å for C3. The ester moiety is in a clear equatorial position (Figure 6a). As observed for the parent valerolactam (CSD code: HIQJOJ)¹¹ two molecules of **5** form an $R_2^2(8)$ amide dimer via N-H \cdots O hydrogen bonds (Figure 6b). The dimerized lactams are connected via C-H \cdots O interactions between C4 and the carbonyl oxygen forming bands in the direction of the *b* axis. Further interconnection occurs by rather weak C-H \cdots O contacts in the *c* direction and hydrophobic interactions between the bands (Fig. 6c).

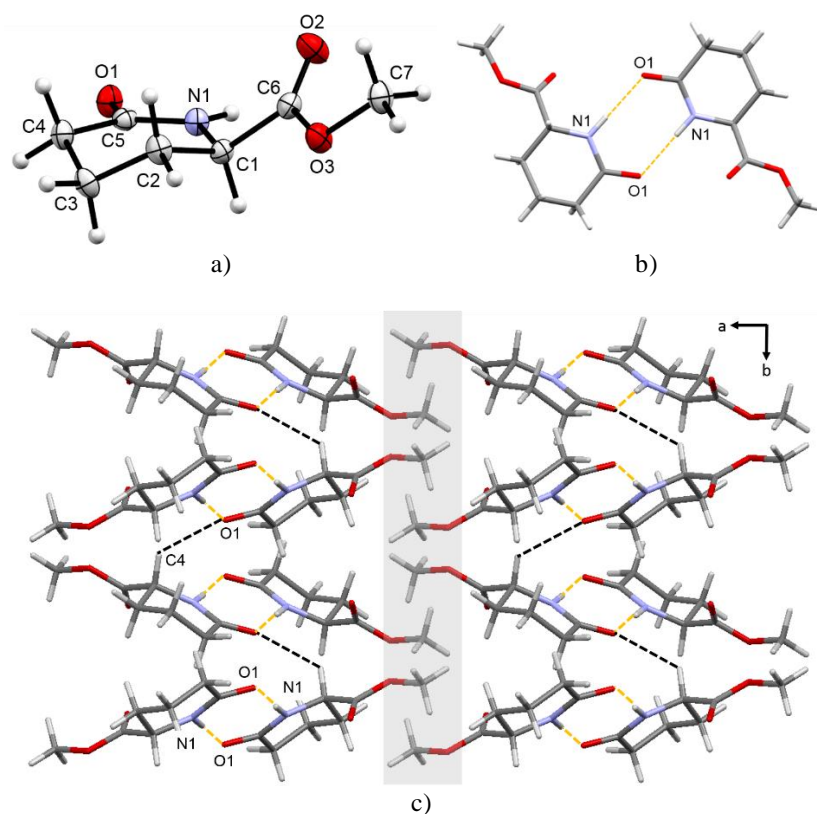


Figure 6. Molecular structure (a) and dimer formation in **3** showing the $R_2^2(8)$ hydrogen bonding motif (b). When viewing the packing down the c axis a combination of strong N-H...O and weaker C-H...O hydrogen bonds is evident; hydrophobic interactions have been shaded in grey (c).

The conformation of pyrohomoglutamic acid (**4**), *i.e.* the N_α carboxylic acid of valerolactam, is very similar to those of the parent compound. The molecule is in the typical half-chair with atoms C2 and C3 deviating from the amide mean plane by 0.463(3) and 0.278(3) Å. The COOH unit occupies an axial position (Figure 7a). In the packing of **4**, two main interactions have been found: 1. The carboxylic acid is engaged in C(7) chains formed by strong O-H...O hydrogen bonding interactions with the amide carbonyl. 2. These chains are interconnected by $R_2^2(8)$ amide dimers via N-H...O hydrogen bonds. The latter are rather weak in comparison to those of the other lactams. This is not only expressed by the longer donor-acceptor distance, but also by the low angle of 152.2(16)°. It leads to a displacement of the participating amide regions of 0.872 Å (Figure 7b). In addition to the strong hydrogen bonds, the O-H...O chains are further interconnected by two C-H...O contacts with the graph set descriptor $R_2^2(8)$ for C4...O3 and $R_3^2(9)$ for C1...O2. The formed sheets are linked by two more C-H...O contacts involving C1...O1 and C2...O3 (Figure 7c).

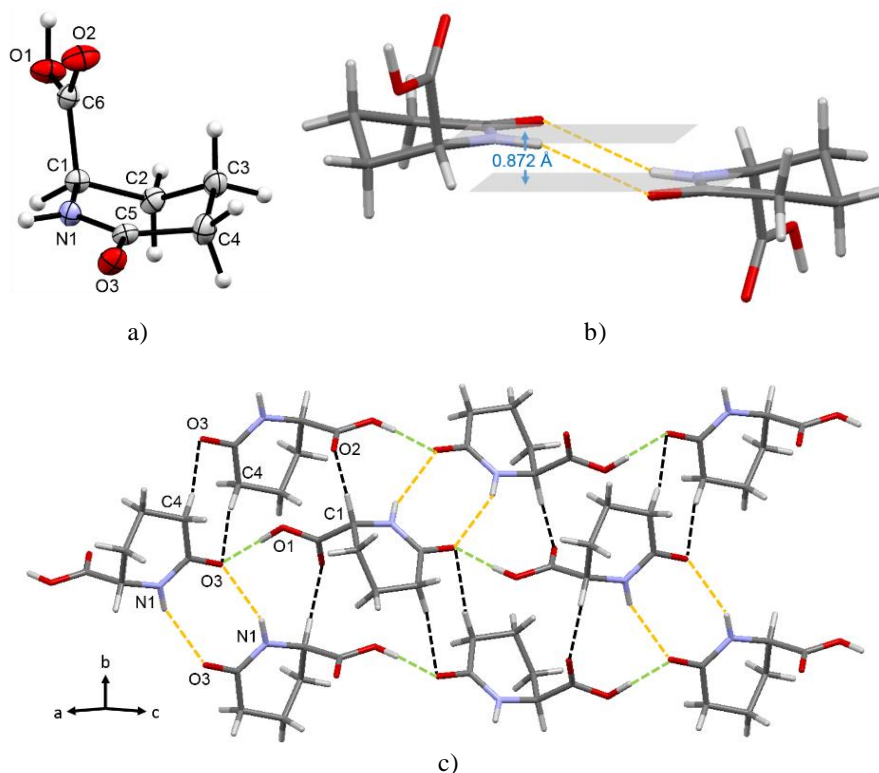


Figure 7. a) Molecular structure of **4**. b) Formation of displaced $R_2^2(8)$ dimers in **4**. c) Packing diagram featuring a combination of $NH\cdots O$ and $OH\cdots O$ hydrogen bonds.

The C(7) graph set descriptor featuring $O-H\cdots O$ hydrogen bonds seems to be a rather dominating interaction for other pyrohomoglutamic acids and is also found in respective *N*-alkylated species (CSD codes: WALWOY,⁶³ LOQCOL,⁶⁴ LOQCUR⁶⁴). Even the loss of the amide proton does not change the strength of $O-H\cdots O$ hydrogen bonds significantly (2.574–2.560 Å).

Caprolactam 5. The conformational behavior of caprolactams is closely related to those of cycloheptene⁶⁵, existing in a symmetrical (pseudo) chair, a symmetrical boat, a twist-boat and a biplanar form⁶⁶, with the chair being lowest in energy. Caprolactam **5** occupies a chair and its conformation is only slightly deviating from the one known for the parent caprolactam (CSD code: CAPLAC⁶⁷). The largest difference is observed for the C6–N1–C1–C2 torsion angle [$59.3(2)^\circ$ vs. 67.8°] (Figure 8a). The additional N_α methyl group in **5** has also no significant influence on the amide bond length compared with the caprolactam methyl ester (CSD code: BOLHER⁴⁹).

In **5**, the ester pendant occupies an axial position. In the packing, $R_2^2(8)$ amide dimers connected via $N-H\cdots O$ hydrogen bonds can be found (Figure 8b). By way of interest, the position of the ester supersedes its size in terms of direct influence on H bonding strength. With the ester moiety in an axial conformation such as in **5** or the monodesaturated methyl ester (CSD code: BOLJIX⁴⁹) the $N-H\cdots O$ distances are comparable to those in the parent caprolactam. For the caprolactam methyl ester (BOLHER) featuring an equatorial ester unit the dimerizing hydrogen bonds are significantly weaker. In the packing the lactam dimers are engaged in a series of $C-H\cdots O$ contacts involving C2 and C5 and all three oxygen atoms (Figure 8c)

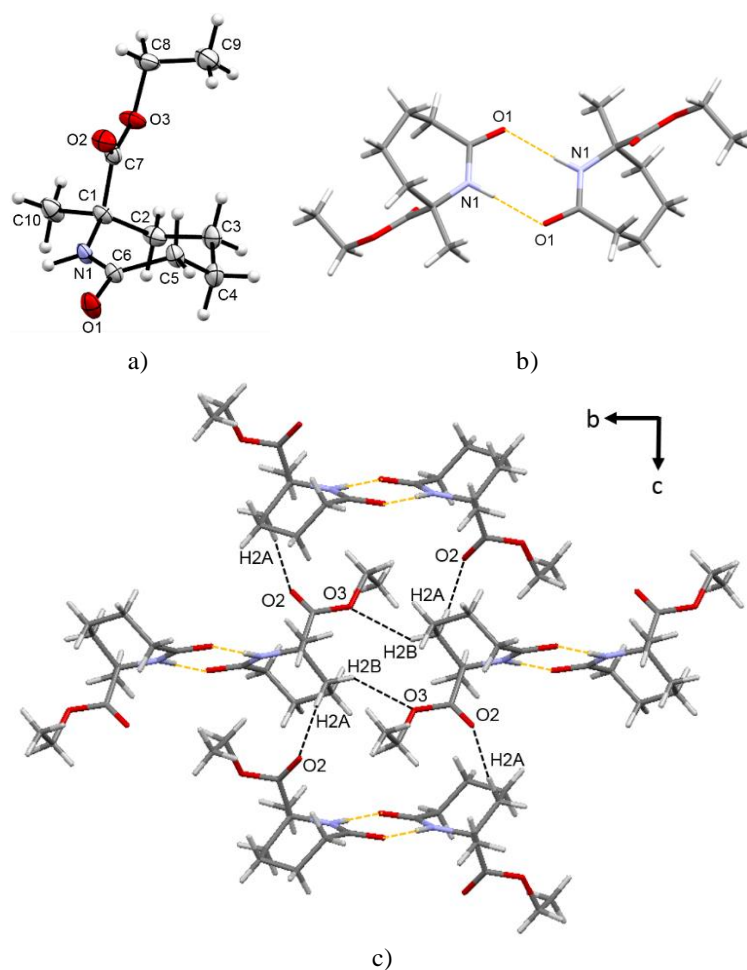


Figure 8. a) Molecular structure of **5**. b) Formation of displaced $R_2^2(8)$ dimers. c) Packing diagram of **5** featuring a combination of $NH\cdots O$ and $CH\cdots O$ hydrogen bonds.

Enantholactams 6-8. All title lactams have been synthesized in a symmetric synthesis, i.e. they occur as racemates in solution. In most cases this leads to the formation of racemic crystals. However, for enantholactams **6** and **8** we observed the formation of conglomerates.

The overall conformation of enantholactam methyl ester **6** is rather close to the one of the parent enantholactam (CSD code: ENANOL⁶⁸) as demonstrated by the similar torsions angles. The ester pendant was found in an equatorial position (Figure 9a). In general, for (enantho)lactam derivatives two hydrogen bonding patterns can be found in the literature: $R_2^2(8)$ amide dimers^{69,70} and $C(4)$ chains.⁷¹ However, in case of methyl ester **6** we found a third possible variation. The amide hydrogen is engaged in a quite weak $N-H\cdots O$ hydrogen bond with the methoxy oxygen of the ester moiety (Figure 9b). This is rather unexpected since OMe oxygens are usually considered weaker acceptors than carbonyl oxygens, of which two can be found in the molecule. The amide carbonyl is engaged in a trifurcated $C-H\cdots O$ contact ($C1\cdots O1$, $C2\cdots O1$, $C6\cdots O1$), whereas the ester carbonyl is involved in a bifurcated one ($C6\cdots O2$, $C9\cdots O2$). The donor-acceptor lengths of the trifurcated contact (four-center contact) found in **6** are shorter and the respective DHA angles much larger than for related systems.⁷²⁻⁷⁴ The overall packing can be described as a combination of two $R_2^2(8)$ $N-H\cdots O/C-H\cdots O=C$ heterodimers.

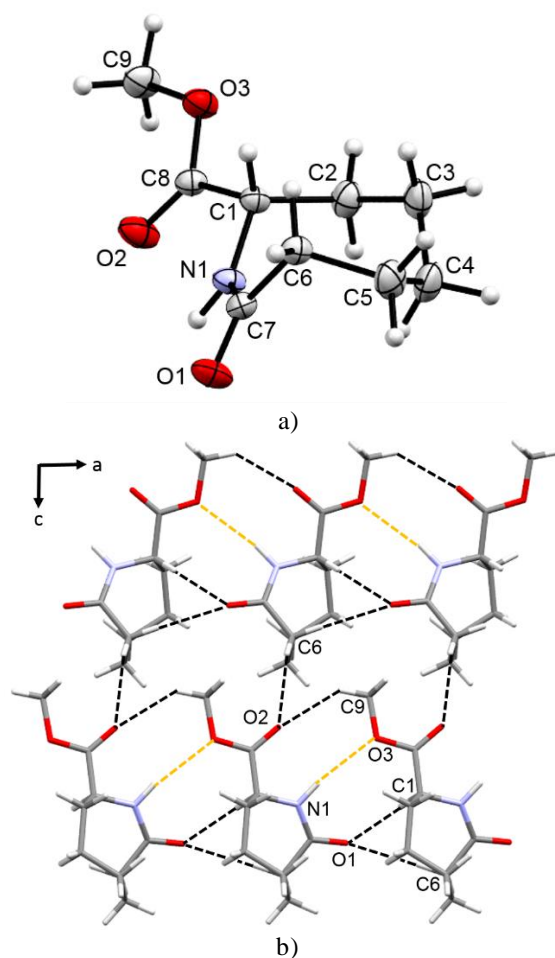


Figure 9. a) Molecular structure of methylester **6**. b) The combination of discrete NH...O hydrogen bonds and a series of CH...O contacts in **6** is in contrast to the packing of the other title lactams.

Title compound **7** has two molecules in the asymmetric unit representing the two enantiomers; the conformations of both differ only slightly. A comparison of ethyl ester **7** to the parent lactam and methyl ester **6** shows distinct variations in their respective conformations with a difference in torsion angles of about 15–20°. Moreover, the amide region is no longer coplanar as in ENANOL, though develops dihedral angles of $-13.7(2)^\circ$ and $14.7(2)^\circ$, respectively. The COOEt unit is in an equatorial position for both molecules of the asymmetric unit (Figure 10a). As observed for the parent lactam the amide units of **7** are engaged in chains of strong N-H...O hydrogen bonds best described with a C(4) graph descriptor, which is usually more typical for *trans* amides.⁷⁵ By way of interest the DHA angle is much lower than observed for the unsubstituted enantholactam. In the overall packing of **7** the N-H...O chains are interconnected by a series of weaker C-H...O contacts. This includes a bifurcated contact (C11...O2, C16...O2), an $R_2^2(6)$ dimerization involving two ester groups (C9...O6, C19...O3) and a very weak carbonyl/ester linkage (C10...O4, C20...O1) (Figure 10b; Figure S2, Supporting Information).

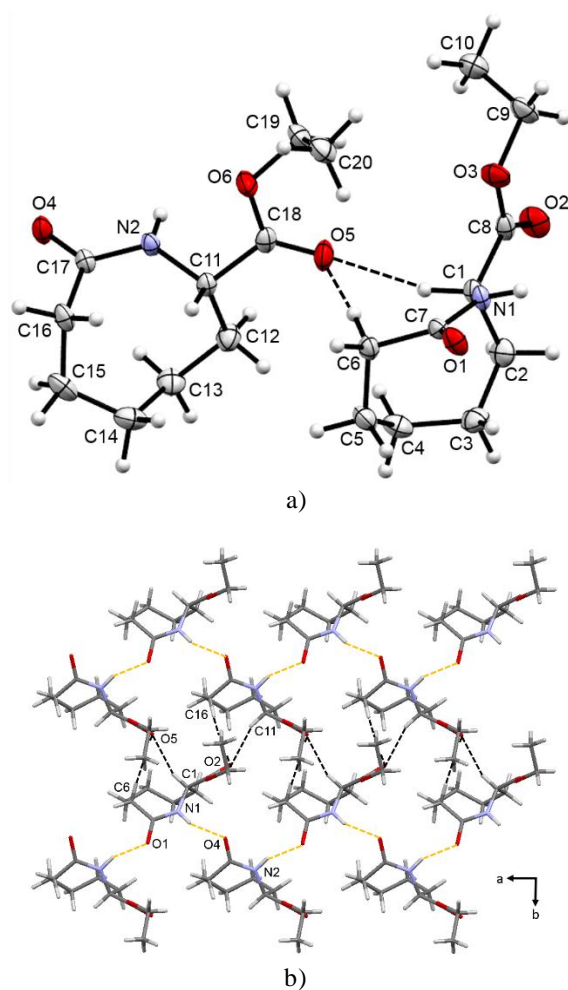


Figure 10. a) Molecular structure of **7**. b) Packing diagram of **7** featuring a combination of NH \cdots O hydrogen bonds and CH \cdots O contacts.

The introduction of the Boc group to enantholactam **7** does not change the equatorial position of the COOEt unit in title compound **8** unlike as observed for the smaller lactams. Though, the dihedral angle of the amide region increases to $-27.9(3)^\circ$; the conformational changes in the rest of molecule are less pronounced (Figure 11a/b). Due to the lack of strong H bond donors the non-covalent interactions in the packing is reliant on a series of C-H \cdots O contacts (Figure 11c).

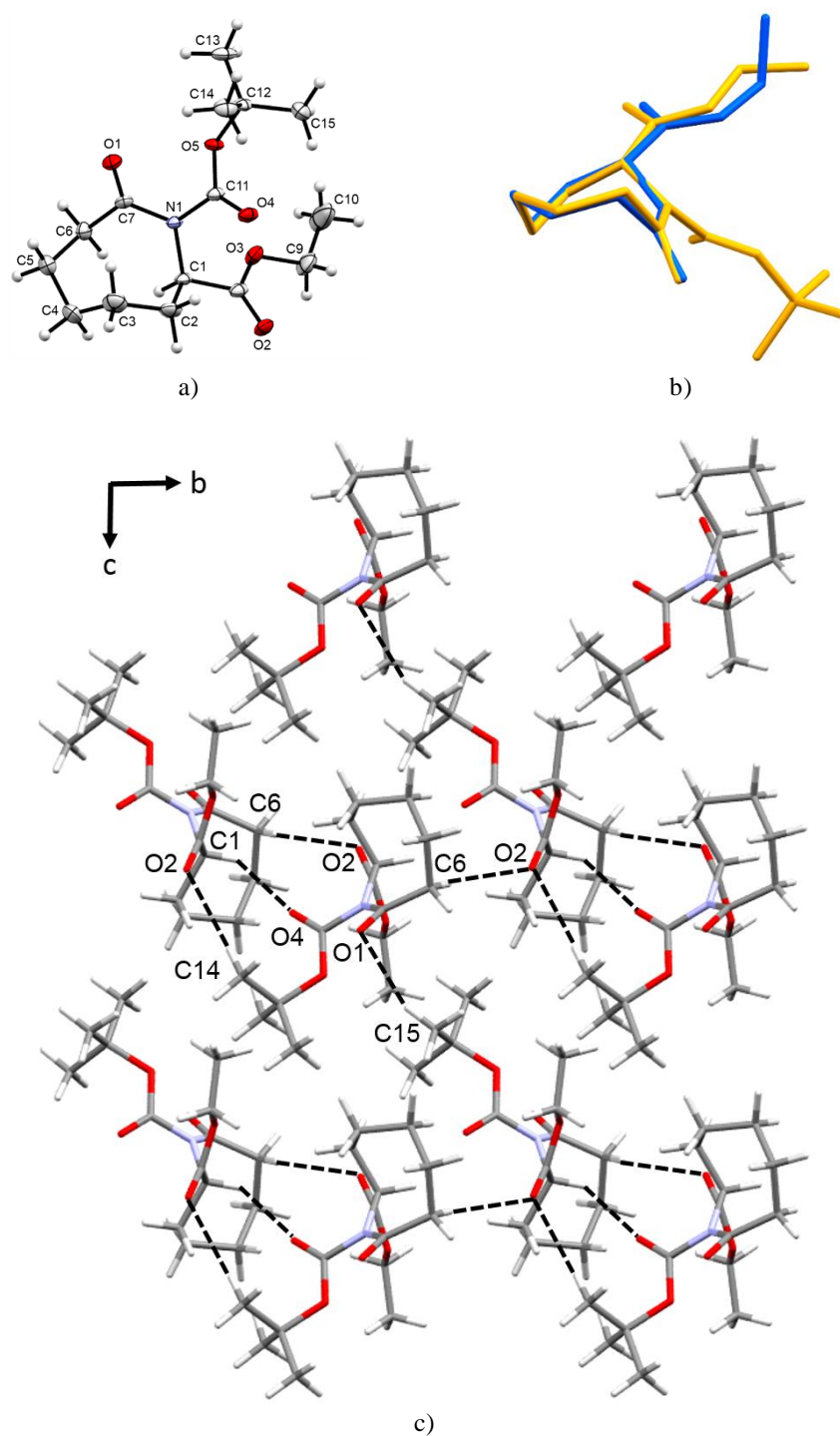


Figure 11. a) Molecular structure of **8**. b) Overlay of ethylester **7(1)** (blue) and the respective bocated compound **8** (orange) (overlay of amide region). c) Packing diagram of **8** highlighting the intermolecular C-H \cdots O contacts.

The relationship of the ester position and reactivity has studied for caprolactam ester **12** and enantholactam ester **8**. While **12** featuring an axial ester undergoes a transannular Dieckmann cyclization when treated with the strong base lithium bis(trimethylsilyl)amide (LiHMDS),¹⁹ the enantholactam **8** with its equatorial ester shows no reaction. We suppose that the switch from axial (**12**) to equatorial (**8**) is a main reason for this behavior (Figure 12).

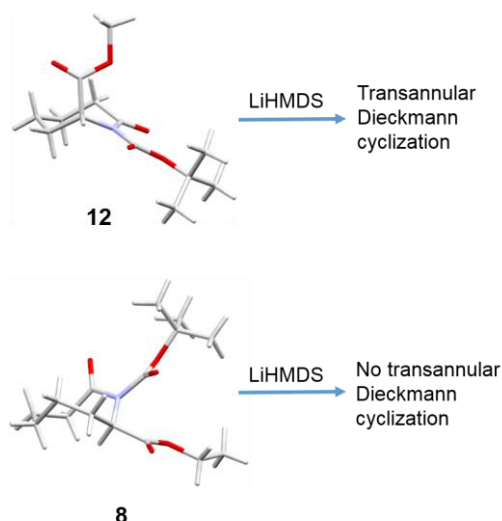


Figure 12. In comparison to caprolactam ester **12** enantholactam ester **8** does not undergo a transannular Dieckmann cyclization reaction leading to a bicyclic system (cf. Figure 3).

Comparison of N_α carboxylated lactams. In order to put our findings in context to the literature, we analyzed published X-ray structures of related lactam acids and respective esters featuring a COOR (R=H, alkyl) in the N_α position (Figure 13). A comprehensive structural analysis can be found in the Supplementary Information (Table S3-S7, Supporting Information).

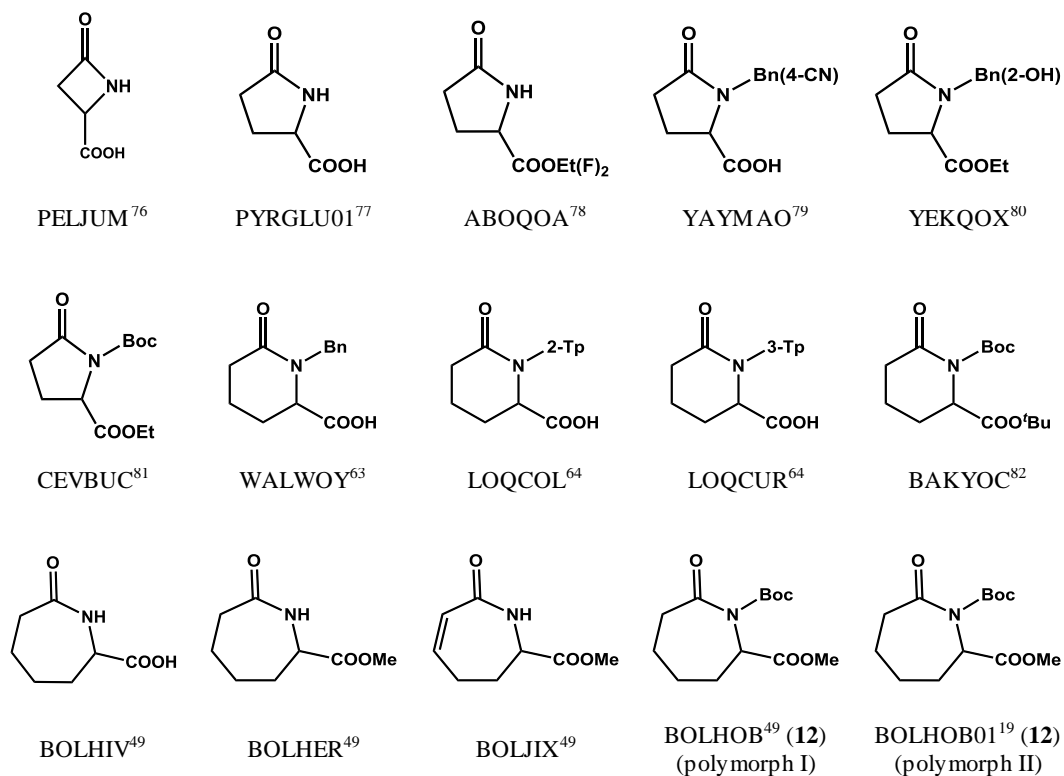


Figure 13. Reference compounds and their CSD refcodes.

Butyrolactams. The envelope conformation of the butyrolactams discussed herein varies for different molecules, which is demonstrated by the broad range of deviation of carbon atom C2 from the mean amide plane (7.4-28.4 °). For the free acid and the difluoroethyl ester the carboxyl pendant prefers an equatorial position, for larger esters and *N*-substituted butyrolactams (Bn, Boc) it occupies an axial position. The butyrolactams with smaller ester residues were found to crystallize as $R_2^2(8)$ amide dimers, those with larger ester residues as C(4) chains. Worth noting, esters of pyroglutamic acid have smaller Kitaigorodskii Packing Indices (KPIs) than the free acid (72.6 %) and the respective parent lactam (71.8 %).

Valerolactams. The ethyl ester moiety of valerolactam takes an equatorial position, whereas in the free acid and in *N*-derivatized (aryl, heteroaryl, Boc) acids and esters the carboxylate is clearly axial. The highest KPI is observed for the methylester and free acid (both 73.5 %). The free valerolactam and the methyl ester is engaged in $R_2^2(8)$ amide dimers; the free acids are engaged in C(7) chains between amide carbonyl and OH group of the acid function.

Caprolactams. In the series of caprolactam carboxylates only the methyl ester and the acid were found as equatorial conformers; desaturation, second N_α substitution and *N*-derivatization lead to axial ester units. The highest KPI has been found for the methylester (72.4 %). Except for the acid all other caprolactams studied here – all of them are small esters – form $R_2^2(8)$ dimers.

Enantholactams. Neither different ester residues (Me, Et) nor *N*-Boc-protection nor different packing modes seem to influence or change the equatorial COOR position. In comparison to the other lactams, the enantholactam esters have very similar torsion angles [149.11(4)-154.6(2) °], though their amide regions loose co-planarity with increasingly sized ester residues. The parent lactam and the ethyl ester form C(4) amide chains; for the methyl ester we were able to describe an alternative packing mode. The parent enantholactam has the highest KPI (70.7 %).

Full comparison of all lactams studied. It is worth noting that none of the lactams studied by X-ray diffraction in this paper contain solvent molecules. One possible explanation is the rather high degree of amide self-aggregation in solution,⁸³ preventing strong interactions of the lactam with solvent molecules. The lengths of the amide bonds in the diverse ester derivatives only vary slightly (1.31-1.35 Å) – indifferently from ring size or carboxy substituent. The only exceptions are the *N*-Boc lactams (imides) with ‘amide bonds’ of 1.39 to 1.42 Å (Figure 14). The largest deviation from the parent lactam to ester is observed for the two Boc-caprolactam polymorphs of **12** (6.14 % / 6.68 %).

The longer amide bond in *N*-Boc protected amides may have influence on the synthetic usability of the respective compounds. While the lactam ester BOLHER (Figure 12) – featuring an amide bond length of 1.347 Å – can be rather easily transferred into the free lactam acid using LiOH in THF/H₂O,⁴⁹ the longer amide bond in **12** may give rise to a hydrolytic ring opening under the same conditions (Scheme 1). (Details on the X-ray structure of the resulting diacid are given in the Supporting Information.) However, structural and hydrolytic studies for the unsubstituted parent lactams have shown, that not differences in the amide bond length are responsible for their varying hydrolytic behaviour.^{11,12} In fact, the formation of the tetrahedral intermediate – connected to the overall conformation of the lactam and potential substituents – was shown to be rate-determining not so much the fission of the C-N bond. So it cannot be ruled out that also the axial or equatorial position of the N_α substituent has an influence on the rate of lactam hydrolysis.

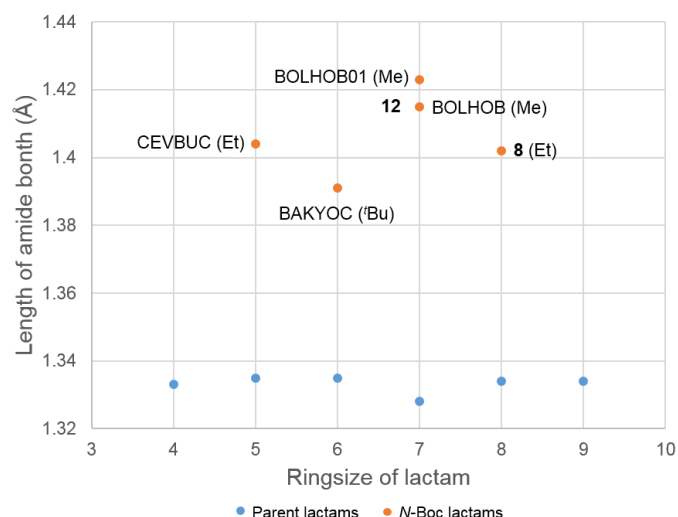
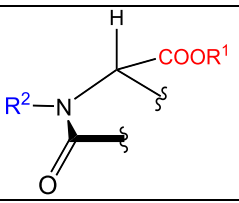
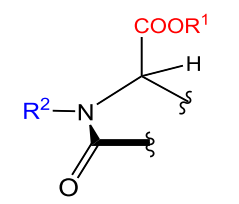


Figure 14. Comparison of the amide bond lengths in *N*-Boc protected esters of different ring sizes (orange) and the respective parent lactams (blue). (CSD codes and the alkyl residues of the esters are shown.)

In the following we studied the influence of N_α carboxyl lactams substitution pattern on the position of COOR unit. There seems to be a tendency, that for ring sizes 5-8, smaller esters (Me, Et, Et(F)₂) and the respective acids prefer an equatorial position (exception: valerolactam acid **4**); larger ester (*i*Pr, *t*Bu) were found to occupy axial sites. For ring sizes 5-7 the *N*-substitution leads an axial arrangement the COOR pendant, as also observed for desaturation and N_α methylation (for caprolactams). For all enantholactams studied the ester moiety occupied an equatorial position (Table 1).

Table 1. Influence of the substitution pattern of N_α carboxyl lactams on the position of the COOR residue

	5	6	7	8
	$R^1=H, R^2=H$ $R^1=Et(F)_2, R^2=H$	$R^1=Me, R^2=H$	$R^1=H, R^2=H$ $R^1=Me, R^2=H$	$R^1=Me, R^2=H$ $R^1=Et, R^2=H$ $R^1=Et, R^2=Boc$
	5	6	7	8
	$R^1=iPr, R^2=H$ $R^1=tBu, R^2=H$ $R^1=H, R^2=Bn(4-OH)$ $R^1=Et, R^2=Bn(2-OH)$ $R^1=Et, R^2=Boc$	$R^1=H, R^2=H$ $R^1=H, R^2=Bn$ $R^1=H, R^2=thiophen-2-yl$ $R^1=H, R^2=thiophen-3-yl$ $R^1=tBu, R^2=Boc$	$R^1=Me, R^2=H$ (monodesaturated) $R^1=Et, R^2=H$ (N_α methylated) $R^1=Me, R^2=Boc$	---

Also with respect to the hydrogen bonding systems we want to hypothesize that at least medium-sized free lactams (ring size 5-7) and small esters (Me, Et, Et(F)₂, *i*Pr) will form $R_2^2(8)$ amide dimers. Larger esters and enantholactam esters prefer C(4) chains. Such a switch from amide dimers to chains has already been observed for the parent lactams.¹¹ The enantholactam methyl ester (**6**) should be seen as an exception in conjunction with the sizes of the lactam ring and the ester.

For all lactam acids discussed here we found O-H...O chains involving the hydroxyl group of the acid and the amide carbonyl; C(7) has been found as a common graph-set motif. For lactam acids featuring free NH functions, additional C=O...HN hydrogen bonds lead to the cyclic motifs $R_3^3(13)$ (ring size: 4; PELJUM), $R_2^2(10)$ (ring size: 5; PYRGLU01) or $R_2^2(8)$ motifs (ring size: 6; 4) (Figure 15). The respective caprolactam acid is an exception: here the molecules are arranged $R_2^2(8)$ acid-amide heterodimers, which are typically only observed for amide/carboxylic acid co-crystals.^{84,85}

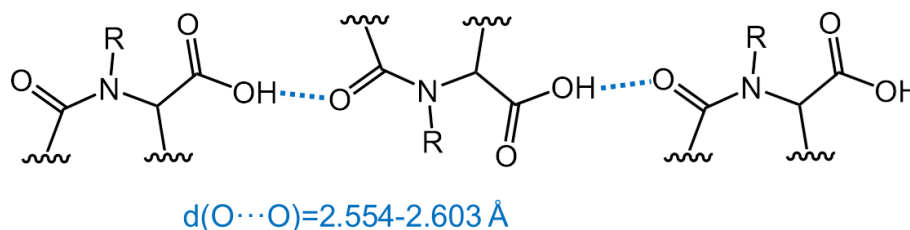


Figure 15. General hydrogen bonding motif found for N_α carboxylactams (except for the respective caprolactam). Depending on the nature of R, the C(7) chains are further interconnected: R \neq H: no other strong hydrogen bonds; R = H: further interactions via N-H...O bonds.

CONCLUSION

In this paper we presented a series of N_α substituted lactams esters and acids with respect to their overall conformation and hydrogen bonding pattern. In total, eight lactams have been synthesized and studied. In addition to the two literature-known amide packing motifs, i.e. $R_2^2(8)$ amide dimer and C(4) amide chain, a third graph-set was found: $R_2^2(8)$ N-H...O/C-H...O=C heterodimers. Additionally, C(7) O-H...O chains has been pinpointed as a typical graph-set motif for the lactam acids. With respect to the overall packing of the lactam ester it can be stated that it is rather rich in C-H...O contacts. In most title compounds the slightly acidic carbon atom C1 is engaged in such contacts ranging from 3.226(3) Å (8) to 3.440(2) Å (2). This correlates with the importance of C_α -H...O contacts for the stability of protein structures.⁸⁶

For comparison reasons, we also included a number of already published lactam esters and acids in our considerations. In general, it can be stated that none of the lactams' X-ray structures contain solvents molecules. To our surprise, the length of the amide bonds does not seem to be majorly influenced by different substituents unless the electron withdrawing *N*-Boc-protection group is introduced. We also found a higher susceptibility towards hydrolytic ring opening, which may go in conjunction with the elongated amide bond. In general, N_α ester moieties have a preference to equatorial occupation for smaller ester as well as their free acids and axial occupation for larger ones. In the same way *N*-substitution leads to an axial arrangement the COOR pendant for ring sizes 5-7; in all enantholactam derivatives studied the ester units occupy equatorial positions. With regard to the crystal packing small esters of the medium-sized lactams seem to prefer the formation of $R_2^2(8)$ amide dimers whereas larger esters and enantholactams form C(4) amide chains. In our opinion the formation of $R_2^2(8)$ N-H...O/C-H...O=C heterodimers in 6 should be considered as exemption in lactams. We will test out this principle in further experiments in order to establish if the exception proves the rule or if N-H...O/C-H...O=C heterodimers are recurrent synthons in lactam structures.

ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic data files (CIF) for **1-8** and **13**. Selected details of the data collection; table of distances and angles of inter- and intramolecular contacts and additional figures and tables underlining the structure description. ^1H and ^{13}C NMR spectra of compounds **1-8** and **13**. The Supporting Information is available free of charge on the ACS Publications website at DOI: [xxx](#)

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Notes

The authors declare no competing financial interest.

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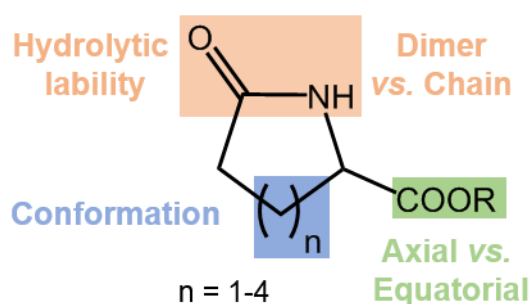
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For Table of Contents Use Only

“Does the exception prove the rule? - A comparative study of supramolecular synthons in a series of lactam esters”

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A series of simple N_α -substituted lactam esters and carboxylic acids is studied with respect to bond length, overall conformation and hydrogen bonding pattern. In addition to the two common amide packing motifs, i.e. the $R_2^2(8)$ amide dimer ($NH\cdots O/NH\cdots O$) and the $C(4)$ amide chain, a third graph-set was found: the $R_2^2(8)$ $NH\cdots O/CH\cdots O=C$ heterodimer.